**How symptoms of mTBIs/ concussions and biomarker levels lead to fast and accurate diagnosis**

Author: Wesley Tanner Cole  
Major: Microbiology  
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

**Key Words:**

Concussions, mTBI, biomarker, microbiome

**This paper will investigate how diagnosis and symptoms of concussions can affect the body, as a whole, down to the cellular level, based on the findings of Jones and Jarvis. The occurrence of concussions has become a widespread epidemic due mainly to individuals being involved in sporting events. Without a method to diagnose and treat effectively, concussions could change how sports are played forever. Since most treatment and diagnosis is strictly subjective to the patient, accurate diagnosis is very difficult to accomplish. Treatment and diagnostic tools are still being developed in hope of figuring out how to treat this injury and minimize the detrimental effects of it. A patient must exhibit no signs of impairment to be cleared of a concussion. In other words, to be “healed” after sustaining a concussion, one must be completely asymptomatic. This paper will examine how these proposed treatments and diagnostic tools affect the body, which is a very important factor in determining if a treatment or tool is worth the side effects. There are many proposed treatments and diagnostic tools that are being researched. The main goal of these diagnostic tools and treatments is to remove the subjective aspect of diagnosing the injury.**

**Introduction**

A concussion or mild traumatic brain injury (mTBI) can happen to anyone. According to the CDC, “A concussion is a type of traumatic brain injury—or TBI—caused by a bump, blow, or jolt to the head or by a hit to the body that causes the head and brain to move rapidly back and forth. This sudden movement can cause the brain to bounce around or twist in the skull, creating chemical changes in the brain and sometimes stretching and damaging brain cells.” The brain can be compared to a plate of jello. When the plate is moved and stopped quickly, twisted, or any other quick movement, the jello moves around, much like the brain would. However, the plate of jello is not encased in the skull like the brain is. When these actions take place, the brain hits the walls of the skull, causing inury and impairment of the brain. The symptoms of a concussion vary, but can include: retrograde amnesia, loss of consciousness, vomiting, dizziness, pressure in head, not feeling right, and personality changes. Most of these symptoms mentioned can not be objectively measured, so treatment can be very difficult if the patient does not tell the truth.

When it comes to diagnosing and treating a concussion, the information is always changing, as the medical profession is still not as knowledgeable on this injury as it is on many others. Once better diagnostic tools are created, treatment can be improved to attempt to take the subjective aspect out of treatment. However, just like many other diagnostic tools and treatments for other medical issues, these can have an effect (good or bad) on the body. Different methods of testing for and treating a concussion have to circulate through the body before going directly to the brain, where the injury has occurred.

**Recent Progress**

Depending on what the treatment or diagnostic tool is, these can have an effect on the cells and microbiome of the body. Some of the cells of the body could also be used to diagnose a concussion due to the presence of them in the blood or elsewhere in the body, where they typically are not found. Jones and Jarvis published a review paper over some of the new methods of diagnosing a concussion. The researchers group types of biomarkers (a biological material present in an organism that if found can lead to a diagnosis) into three distinct categories: Neuronal injury biomarkers, Axonal injury biomarkers, and Astrocyte injury biomarkers. Neurons are a type of cell prevalent throughout the body. These cells are nerve cells and only nerve cells. Neurons work off of electrical impulses/ signals to transport information to the brain. The biomarkers included in the Neuronal injury biomarkers are NSE and UCH-L1. Axons are parts of the neuron. This part of the neuron helps to conduct and transport electrical impulses from one neuron to the next. The biomarkers included in the Axonal injury biomarkers are: Alpha-II SBDPs, Tau proteins, and Neurofilaments. Astrocytes are star-shaped, non-neuronal cells that provide support and protection to neurons. They assist cells that form the blood-brain barrier. Astroctyes also assist in biochemical and nutrient regulation of neurons and help with the healing process of the nervous system after injury has occurred. The biomarkers included in the Astrocyte injury biomarkers are S100β and GFAP.

**Discussion**

Each of the afore mentioned biomarkers has its own strengths and weaknesses of what makes it a useful diagnostic tool. Jones and Jarvis set out to find which biomarker(s) is the best fit for reliable diagnosis of a concussion. Most of the research and compiling of research that Jones and Jarvis performed was based on the prevalence in recent publications of whichever biomarker they were looking at. They also looked at the amount of each biomarker found in particular places of the body after an injury was sustained.

The Neuronal injury biomarker category contained two distinct biomarkers that are unique to neurons. **NSE**, or neuron specific enolase, is an enzyme unique to the nervous system. This enzyme has been found to be elevated in the blood after a neuronal injury has occurred. This biomarker has been found in patients with a severe TBI at 72 hours after injury has occurred. However, upon further research Jones and Jarvis found that **NSE** levels appear to not be a good biomarker to be used for a diagnostic tool. **UCH-L1**, or ubiquitin C-terminal hydrolase isozyme L1, is a protein found in neurons that assists with metabolism of ubiquitin. This biomarker has been found in patients with mild/moderate TBI an hour after injury has occurred. This biomarker seems to be able to distinguish between patients with an mTBI and those who do not have one.

The Axonal injury biomarker category contains three diverse biomarkers that are unique to not only neurons, but specifically to axons. **Alpha-II SBDPs**, or alpha-II spectrin breakdown products, is a major component of the cytoskeleton of the axon. This biomarker has been found in elevated levels of patients with severe TBIs. It was also found that levels of this biomarker were greater in patients with severe to moderate TBIs compared to patients with no injury. However, there was no such correlation for patients with mTBIs. **Tau Proteins** are intracellular proteins that are responsible for microtubule bundles and transport within axons. This protein is also found in patient with CTE (chronic traumatic encephalopathy), which is a disease that comes from repeated concussive blows to the head. The buildup of this protein due to damage of the brain can lead to cognitive issues. This biomarker has been found in elevated levels in the blood after a TBI has occurred. However, research has shown that this biomarker is a poor diagnostic tool for mTBIs. **Neurofilaments** are responsible for the cytoskeleton of the neuron. After a TBI, a sharp increase in calcium levels within the neuron kicks off a phosphorylation process that assists in causing axonal injury. This process causes neurofilaments to be found in the blood of patients with a TBI. However, research shows that the process of neurofilament level elevation can take up to six hours after injury has occurred. Thus, using this biomarker as a diagnostic tool would not lead to a quick and accurate diagnosis in very acute cases of TBI.

The Astrocyte injury biomarker category has two different biomarkers unique to the nervous system, but not being made up of neuronal cells. **S100β** is a protein found in the cytosol of astrocytes and Schwann cells. This protein specifically is a calcium-binding protein. This biomarker has been found post mTBI when cognitive impairment is present. However, this biomarker has also been found in patients with other injuries that have no brain injury. **GFAP**, or Glialfibrillary acidic protein, helps to make up the structure of astrocytes. This biomarker has been found in eleveated levels of patients with TBIs, and research shows that elevated levels are still present months later in patients who have experienced adverse effects from the injury. Research also shows that this biomarker also begins to be present an hour after injury has occurred.

Out of all the biomarkers mentioned, Jones and Jarvis narrowed the two best choices down to **UCH-L1** and **GFAP**. These biomarkers would work the best due to the quick presence after injury has occurred. These biomarkers are unique to TBIs as well, unlike some of the other biomarkers mentioned. Jones and Jarvis hope that the use of these biomarkers will reduce the amount of radiation the patient’s body is exposed to, since radiation from imaging causes damage down to the cellular and DNA levels. Concussion diagnosis can only work through knowledge of the molecular processes of the body and the cellular components that make it up. Without this knowledge, using these biomarkers for diagnosis would not be possible.

**References**

Alastair Jones, Paul Jarvis. “Review of the potential use of blood neuro-biomarkers in the diagnosis of mild traumatic brain injury.” Clinical Experimental Emergency Medicine. 4 (2017) 121-127

CDC. “What is a Concussion?” <https://www.cdc.gov/headsup/basics/concussion_whatis.html> (2017)

Benjamin H. Wing, Braden J. Tucker, Alina K. Fong, and Mark D. Allen.“Developing the Standard of Care for Post-Concussion Treatment: Neuroimaging-Guided Rehabilitation of Neurovascular Coupling.” Open Neuroimaging Journal. 11 (2017) 58-71

Tan XL, Wright DK, Liu S, Hovens C, O'Brien TJ, Shultz SR. “Sodium selenate, a protein phosphatase 2A activator, mitigates hyperphosphorylated tau and improves repeated mild traumatic brain injury outcomes.” Neuropharmacology. 108 (2016) 382-393